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HUMAN PROSTATE CANCER CELLS LACK FEEDBACK REGULATION OF LOW-DENSITY LIPOPROTEIN RECEPTOR AND ITS REGULATOR, SREBP2

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The low-density lipoprotein receptor (LDLR) pathway provides cells with essential fatty acids for prostaglandin E_2 (PGE_2) synthesis. Regulation of LDLR expression by LDL was compared between the human normal and cancer prostate cells using semi-quantitative RT-PCR and LDL uptake assays. LDLR mRNA expression and LDL uptake by LDLR were down-regulated in the presence of exogenous LDL or whole serum in the normal prostate cells, but not in the prostate cancer cells. Addition of exogenous cholesterol down-regulated both LDLR and a potent regulator of the *ldlr* promoter, sterol regulatory element binding protein 2 (SREBP2), in normal cells but not in cancer cells. PGE_2 synthesis in prostate cancer cells was significantly increased in response to LDL. Our study suggests that over-production of LDLR is an important mechanism in cancer cells for obtaining more essential fatty acids through LDLR endocytosis, allowing increased synthesis of prostaglandins, which subsequently stimulate cell growth. The data also suggest that the sterol regulatory element and SREBP2 play a role in the loss of sterol feedback regulation in cancer cells.

Key words: *LDL receptor; prostate cancer; PGE_2; SREBP2; feedback regulation*

Low-density lipoprotein (LDL) and its receptor (LDLR) have been extensively studied for their critical roles in cholesterol clearance and metabolism.[1] LDLR is a cell surface glycoprotein[2] that binds and internalizes LDL, the major carrier of cholesterol and fatty acids in blood. Sterols or sterol-containing LDL down-regulates expression of LDLR in a number of cell types studied, including fibroblasts,[3,4] lymphocytes,[5,6] hepatocytes[4,7] and granulosa cells[8]. Several studies have reported elevated or ineffectively regulated LDLR expression in different types of cancer. Gueddari *et al.*[9] reported up-regulation of LDLR in the A549 human lung adenocarcinoma cell line when compared with fibroblasts. LDLR is over-expressed in many of the human colorectal cancer biopsies and LDLR feedback regulation is lost in the DiFi colorectal cancer cell line.[10] Decreased feedback regulation of LDLR has been reported in the Daudi Burkitt's lymphoma cells[6] and in acute myelogenous leukemic cells from patients.[11]

LDLR expression is regulated by sterols *via* the sterol regulatory element (SRE-1),[12] which is located at -65/-56 of the *ldlr* gene. This DNA element (5′ ATCACCCCAC 3′) binds to SREBPs, a family of transcription factors that require cleavage before they are released from the membrane-bound precursor molecules and activate gene expression.[13] The *srebp1* gene produces 2 proteins (SREBP1a and SREBP1c) through alternative splicing. SREBP1a has a longer activation domain and is a more potent transcription activator. The less potent SREBP1c is believed to be important in constitutive fatty acid synthesis. SREBP2 is another strong activator encoded by a separate gene. Expression of SREBP2 is stimulated in response to sterol depletion in the liver.

Another function of the LDLR pathway is to deliver essential fatty acids into the cells.[14] Essential fatty acids include linoleic acid (LA) and arachidonic acid (AA). LA can be converted by Δ-6 desaturase into AA, which is the precursor molecule for synthesis of eicosanoids such as prostaglandin E_2 (PGE_2). PGE_2 is synthesized by the cyclo-oxygenases (COX, EC 1.14.99.1). One of the COX isozymes, COX-1, is a constitutively expressed enzyme; the other isozyme, COX-2, is inducible. PGE_2 acts as an autocrine or paracrine factor to induce a variety of physiological responses including cell growth, differentiation and immune regulation.[15–17] In prostate cancer cells, PGE_2 up-regulates COX-2 message and stimulates cell growth,[18] making cox-2 a feedforward enzyme.

Although the role of LDLR in cholesterol metabolism is well understood, study on the association between LDLR regulation and cancer cell growth is lacking. Our study compares the LDLR feedback regulation by LDL and PGE_2 production of normal and cancer prostate cells. We also examined the mechanism responsible for loss of LDLR feedback regulation by comparing the effect of cholesterol treatment on SREBP expression between normal and cancer prostate cells.

MATERIAL AND METHODS

Material

PrEC normal human prostate epithelial cells were obtained from Clonetics (San Diego, CA). The PC-3 and the DU145 human prostate cancer cell lines were provided by the University of California San Francisco (UCSF) Cell Facility (San Francisco, CA). The human normal fibroblasts, GM03348D, and familial hypercholesterolemia fibroblasts, GM02000G, were from Coriell Cell Repository (Camden, NJ). The benign prostate hyperplasia (BPH) cell line was a gift from Dr. Rajvir Dahiya (Veterans Administration Medical Center, San Francisco, CA). FCS was purchased from Hyclone Laboratories (Logan, UT). RPMI medium, glucose and antibiotics were from UCSF Cell Facility. Lipoprotein-deficient calf serum (LPDS), LDL, cholesterol, 25-hydroxycholesterol and Tri-Reagent were from Sigma (St. Louis, MO). RNA PCR kit was from Perkin-Elmer (Foster City, CA). DiI-LDL was purchased from Molecular Probe (Eugene, OR). PGE_2 assay kit was from Cayman Chemical (Ann Arbor, MI).

Cell culture

PrEC cells were maintained in the PrEGM medium (Clonetics). The PC-3, DU145, BPH-1 prostate cell lines and the fibroblasts were maintained in complete RPMI 1640 medium supplemented with 10% FCS, 2 mM L-glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin and 0.25 μg/ml amphotericin B. All cells were cultured with 5% CO_2 at 37°C. For experiments, cells were grown with FCS or LPDS-supplemented LDL or with cholesterol as described in detail in the figure legends.

Semi-quantitative RT-PCR

RNA was isolated from cells using the Tri-Reagent as recommended by the manufacturer and was quantified in the GeneQuant spectrophotometer (Pharmacia, Piscataway, NJ). RT-PCR was carried out in a Robocycler 40 (Stratagene, San

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TABLE I – PRIMERS USED IN RT-PCR REACTIONS

Target	Orientation	Sequence	Product size (bp)
LDLR	Sense	5′ CAATGTCTCACCAAGCTCT	258
	Anti-sense	5′ TCTGTCTCGAGGGGTAGCT	
SREBP2	Sense	5′ GCAGATGGGCAGCAGAGTTCC	629
	Anti-sense	5′ GTGGTCAGGAGGCGGCAATG	
SREBP1c	Sense	5′ GCCAGCAGCTCCATTGACA	493
	Anti-sense	5′ GCCCCTGTGCCCCCTCTC	
COX-2	Sense	5′ GTGCCTGGTCTGATGATGTATGC	724
	Anti-sense	5′ CCATAAGTCCTTTCAAGGAGAATG	
Cyclophilin	Sense	5′ CGTCTCCTTTGAGCTGTTTGCAGAC	628
	Anti-sense	5′ CATAATCATAAACTTAACTCTGCAATCCAGC	
18S	Sense	5′ TCAAGAACGAAAGTCGGAGG	488
	Anti-sense	5′ GGACATCTAAGGGCATCACA	

Diego, CA) using the RNA PCR kit. Conditions for RT-PCR were as described previously.[18] Most of the specific PCR primers for the *ldlr*, *srebp2*, *srebp1c*, *cox-2* and cyclophilin genes (Table I), were designed in this laboratory. The primers were synthesized by Operon Technologies (Alameda, CA). The PCR products were separated by electrophoresis in an agarose gel and the visualized photographs were scanned and quantified using the SigmaGel software (Sigma). Data were analyzed using the SigmaStat software (Sigma). PCR efficiency of the reactions was verified by examining the slopes of the PCR product curves. Housekeeping genes from the same samples were amplified and used as internal standards. The difference between samples measured by semi-quantitative methods, however, does not necessarily reflect the absolute amount of difference of the specific RNA.[19]

DiI-LDL uptake assay

Prior to assay, cells grown on coverslips in 6-well plates were incubated in RPMI medium containing 10% LPDS with 30 μg/ml LDL for 10 min at room temperature. DiI-LDL and Hoechst dye were then added to 10 μg/ml and 50 μg/ml, respectively, and incubated for 1.5 hr at room temperature in dark. Cells were washed twice in PBS containing 1.25 mg/ml BSA and once in PBS. They were visualized and photographed under a Zeiss Axioskop fluorescent microscope (Zeiss, Thornwood, NY). Cell nuclei were stained with Hoechst dye to ensure a similar number of cells present in the photographed field.

PGE_2 assay

An aliquot of culture medium was collected and frozen at -70°C before the cells were harvested for RNA isolation. PGE_2 levels in the culture medium samples were determined by the PGE_2 monoclonal enzyme immunoassay kit following the manufacturer's protocols. This assay kit is highly specific for native PGE_2 and does not detect other prostaglandins. A Dynatech MR5000 microplate reader (Dynatech, Chantilly, VA) was used to read the assay results. Data were analyzed by the BioLinx 2.0 software (Dynatech).

RESULTS

Feedback regulation of LDLR mRNA expression by LDL in human prostate cells

Expression of LDLR is feedback regulated by cholesterol or by LDL, which carries cholesterol in many cell types. In our study, we investigated how LDLR expression was regulated by LDL in human prostate cells. The presence of LDL or whole serum significantly ($p < 0.005$) reduced the LDLR mRNA level (measured by RT-PCR) in the PrEC normal prostate cells, compared with those grown in LPDS (Fig. 1*A*). The PC-3 cancer cells, however, expressed a similar amount of LDLR in the presence or absence of exogenous LDL or serum lipoprotein (Fig. 1*B*). This suggests that

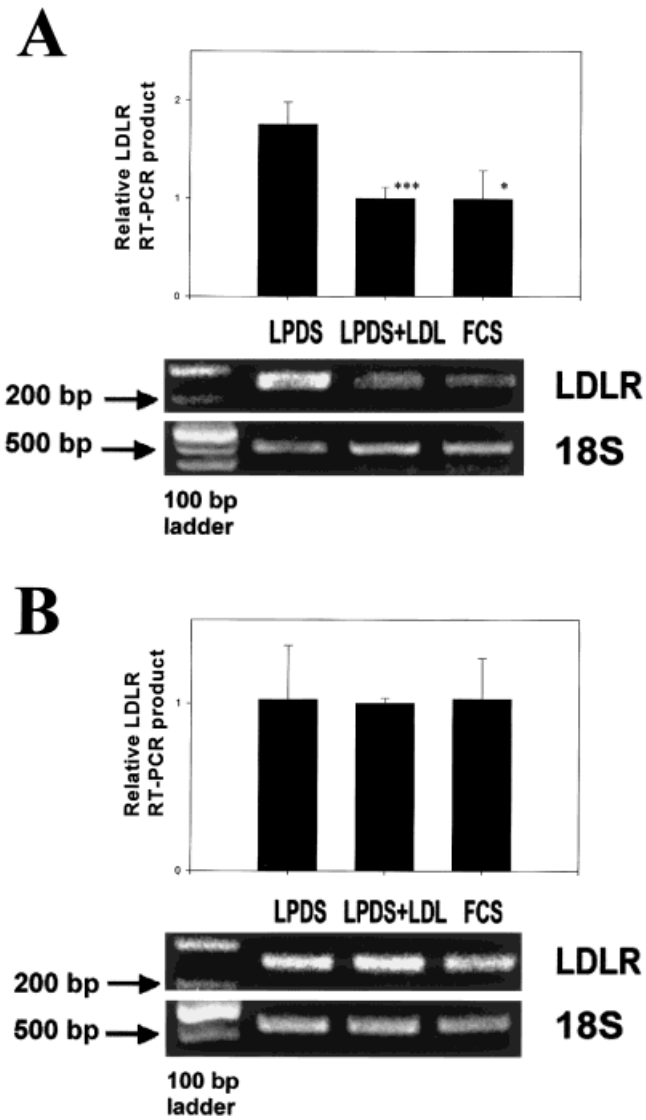

FIGURE 1 – LDLR mRNA expression in human prostate cells. Total RNA from cells grown with 10% LPDS ± LDL (100 μg/ml) or 10% FCS for 45 hr was subjected to RT-PCR with LDLR primers. Each bar in the bar graphs represents mean ± SD of the relative amount of RT-PCR products (normalized to the 18S product) from 3 independent samples. Below the bar graphs are representative PCR bands on agarose gels. The bands in the 100 bp ladder immediately below the PCR products are indicated by arrows at left. (*A*) PrEC cells; (*B*) PC-3 cells. *$p < 0.02$; *** $p < 0.005$

the cancer cells lack normal LDLR feedback regulation at the mRNA level.

Regulation of LDL uptake

To further study the regulation of LDLR expression at the functional level, LDLR activity was measured by uptake of fluorescent-labeled LDL. As shown in Figure 2, the PrEC cells grown in LPDS for 45 hr had strong fluorescent signals, showing active LDL uptake by endocytosis. When cells were grown in the presence of LDL or whole serum, the uptake was much lower. In contrast, LDLR activity (measured by DiI-LDL uptake) remained unchanged regardless of the presence of lipoproteins in the PC-3 prostate cancer cells. A human fibroblast cell line derived from a familial hypercholesterolemia patient, which lacks functional LDLR expression, was used as negative control for LDLR-mediated LDL uptake.

The BPH-1 cell line, which is an immortalized but non-transformed human prostate epithelial cell line,[20] was also included in the LDL uptake experiment. This cell line had a high level of LDL uptake, and LDL or serum lipoprotein failed to down-regulate LDLR expression, suggesting that cells at a benign growth stage may have lost LDLR feedback regulation.

Cholesterol regulation of SREBP and LDLR expression

To understand the role of transcription factors on loss of LDLR feedback regulation in prostate cancer cells, cholesterol regulation of SREBP expression was studied (Fig. 3). In both PrEC cells and normal human fibroblasts, SREBP2 expression was significantly down-regulated by cholesterol ($p < 0.02$). The same feedback was not observed in the human prostate cancer cell lines, PC-3 and DU145. SREBP1c expression was not regulated by cholesterol treatment in any cells tested. A specific SREBP1a product was not amplified from any of the above cell lines even after using 4 different combinations of primers and varying magnesium concentrations in PCR amplification. As expected, cholesterol regulation of LDLR expression was similar to regulation by LDL in both PrEC and PC-3 cells.

LDL increased PGE_2 synthesis in cancer cells

Because the lack of LDLR feedback regulation may enable the cancer cells to acquire more essential fatty acids and increase PGE_2 synthesis, we investigated whether PGE_2 production from LDL was differently regulated in normal and cancer cells. The PGE_2 level of the PrEC culture slightly decreased after 45 hr of incubation with LDL. In PC-3 cells, LDL significantly increased

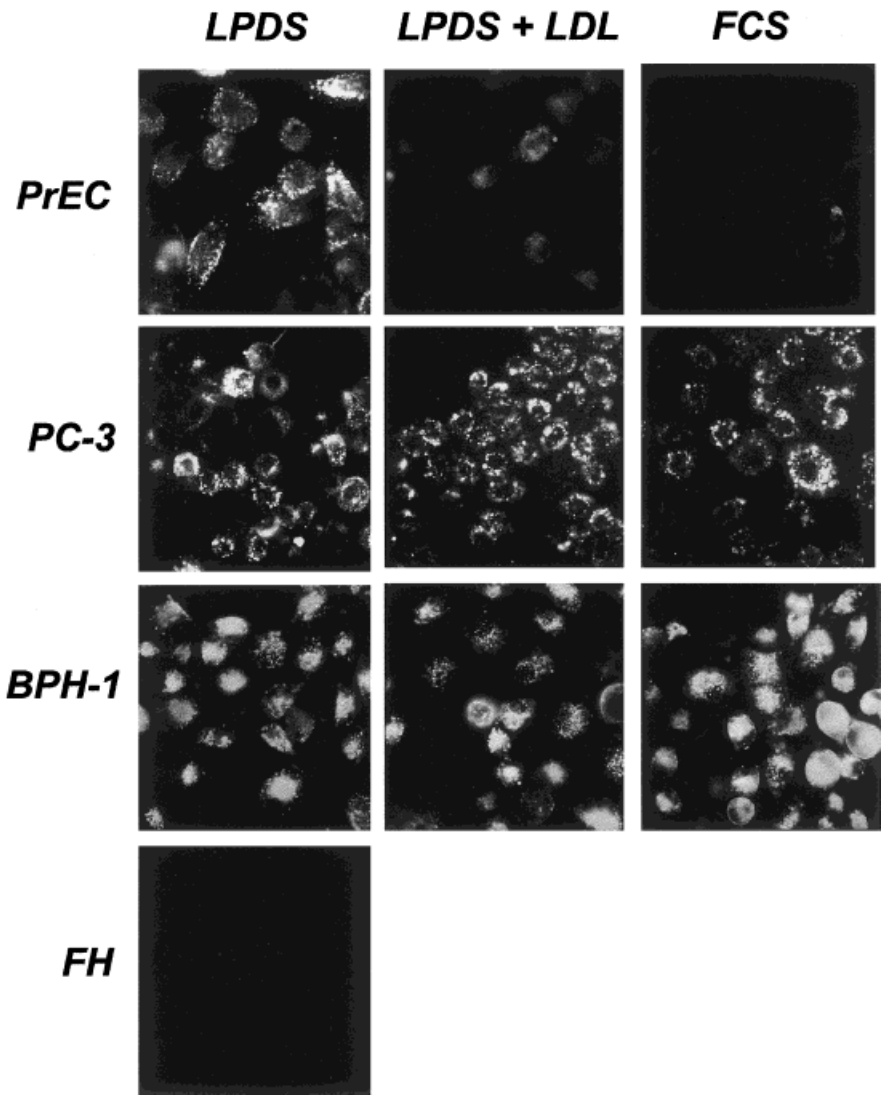

FIGURE 2 – DiI-labeled LDL uptake by human prostate cells. Cells were seeded to coverslips and grown in growth media containing 10% LPDS, 10% LPDS + 30 μg/ml LDL or 10% FCS for 45 hr. They were then labeled by DiI-LDL as described in Material and Methods. Bright areas on the photographs represent DiI-LDL taken by the cells or bound to the cell surface. FH, human familial hypercholesterolemia fibroblasts.

the PGE_2 level (more than 3-fold, Fig. 4). This suggests that the normal prostate cells have a mechanism to regulate PGE_2 synthesis even when a large number of precursor molecules are available. The cancer cells, on the other hand, do not efficiently regulate PGE_2 synthesis from its substrate.

DISCUSSION

Our study demonstrates that expression of LDLR is feedback regulated by LDL in normal human prostate cells, as in other normal cell types. This regulation is lost in the prostate cancer cells. This explains why the PC-3, but not PrEC, cells increased PGE_2 production in response to LDL administration. Lack of feedback regulation in cancer cells has been observed in lymphocytes and colorectal cells, and may be a universal strategy that many cancer cells employ to accelerate their growth. Increased fatty acid uptake by cancer cells resulting from elevated LDLR expression may provide an extra energy source and structural molecules to promote uncontrolled growth. Moreover, it delivers increased amount of essential polyunsaturated fatty acids for synthesis of bioreactive eicosanoids such as PGE_2. Prostaglandins influence cancer development and growth by stimulating cell growth[18] and by their involvement in mutagen generation, tumor promotion and immune suppression (reviewed by Marnett.[16] 5-Hydroxyeicosatetraenoic acid is another eicosanoid metabolite of AA through the lipoxygenase pathway. This molecule has been suggested to be involved in maintaining cancer cell growth, because blocking its synthesis in a human prostate cell line causes apoptosis.[21] In normal cells, the feedback regulation of LDLR restricts the transportation of cholesteryl fatty acids into the cells. The lack of LDLR regulation in cancer cells allows unregulated uptake of high levels of fatty acids when the serum LDL level is high. A previous study also reported up-regulation of COX-2 gene expression by PGE_2 in PC-3 cells.[18] Together, the unlimited fat uptake by LDLR and the increased COX-2 activity may contribute to the increased PGE_2 production by PC-3 cells with a good LDL supply. This suggests that fat, especially if rich in essential fatty acids (precursors for eicosanoid synthesis), may increase the risk for cancer progression. Interestingly, a non-transformed immortal cell line, BPH-1, also lacks feedback regulation of LDLR, as suggested by the LDL uptake assay. We started studies of human prostate normal and cancer biopsies and found an up-regulation in the LDLR in 6 of 12 tumors (data not shown). Further studies in similar cell lines and in prostate epithelial tissues of benign tumors and cancers will help us to understand the lack of feedback regulation in cancer development *in vivo*.

Feedback regulation of LDLR occurs primarily at the transcriptional level,[22] although there is also evidence for post-transcriptional regulation.[4] It is not known how the cancer cells lose feedback regulation of LDLR by sterols. The importance of the SRE-1 in LDLR regulation by sterols suggests that this element may be involved in loss of feedback in cancer cells. An early study by Brown *et al.*[23] demonstrated a lack of feedback regulation of the HMG-CoA reductase by cholesterol in malignant tissues. This further supports the possibility that SRE-1, which is shared by the promoters of the genes encoding HMG-CoA and LDLR, plays an important role in the loss of sterol feedback regulation in cancer cells. Interestingly, the *srebp2* promoter contains a perfect SRE-1, whereas the *srebp1* (which encodes SREBP1a and SREBP1c) promoter does not.[24] Our finding that SREBP2 was feedback regulated by cholesterol in normal cells further supported a role of the SRE-1 in auto-regulation of the *srebp2* promoter. Moreover, the lack of SREBP2 feedback in cancer cells at least in part explains the lack of LDLR feedback in cancer cells. A final understanding of the mechanism for lack of sterol feedback in cancer cells will rely on a complete knowledge of the feedback process and a thorough investigation of *srebp2* promoter regulation.

Our results showed that prostate cancer cells expressed more LDLR molecules than normal cells in the presence of LDL or whole serum. Although the cancer cells benefit from loss of LDLR feedback regulation for their growth, it is possible to use this phenomenon in cancer therapy. Koller-Lucae *et al.*[25] reported that an anti-cancer drug, N^4-octadecyl-1-β-D-arabinofuranosylcytosine, can be incorporated into LDL and taken up by lymphoma cells *via* the LDLR pathway. Because the normal cells express lower levels of LDLR than the cancer cells, especially after being feedback regulated by a high level of sterol, anti-cancer drugs carried by LDL may target more specifically and more efficiently

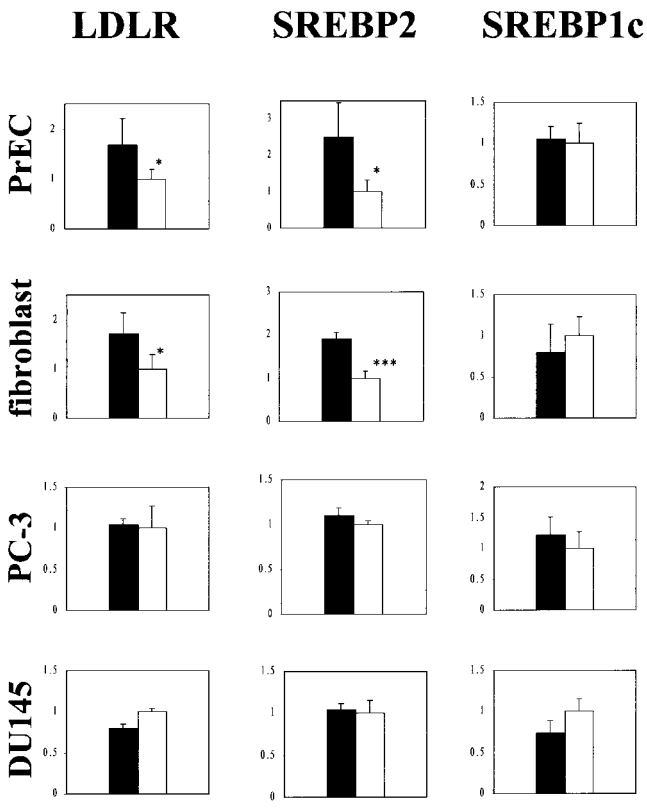

FIGURE 3 – Cholesterol regulation of SREBP and LDLR expression. Cells were grown for 30 hr in media containing LPDS (black bars) or LPDS + 10 μg/ml cholesterol and 1 μg/ml 25-hydroxycholesterol (open bars). RNA was isolated from the cells and subjected to RT-PCR. Amount of PCR product was normalized to that of the internal standard, cyclophilin. Mean and SD shown in the bar graphs represent 3 independent samples. Normal human fibroblasts were used as control. $*p < 0.02$; $***p < 0.01$

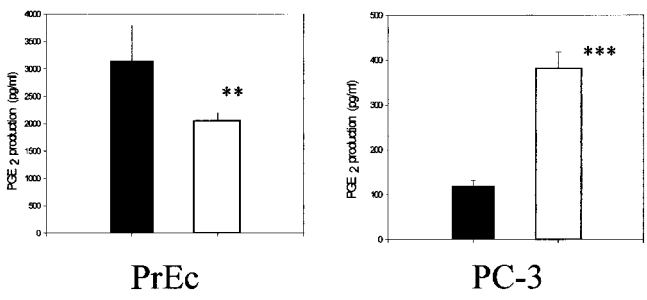

FIGURE 4 – PGE_2 production by human prostate cells. Cells were grown in media containing 10% LPDS (black bars) or 10% LPDS + 100 μg/ml LDL (open bars) for 45 hr. Culture media samples from the cells were assayed for PGE_2 level. The mean and SD of 3 independent samples are shown in the bar graph. ** $p < 0.01$; ***$p < 0.005$

the cancer cells. A thorough understanding of the regulation of LDLR expression in all major types of cells in the human body, and the mechanism for the loss of feedback regulation in cancer cells, will reduce the risk of side effects from such a therapeutic strategy.

Previous experiments have associated dietary fat with the risk of prostate, colon, and breast cancers.[16,26] In studies of colorectal cancer, we have also noted aberrant regulation of LDLR in tumors compared with control biopsies.[10] Inhibitors of the eicosanoid synthesis pathway inhibit cell growth,[27,28] suggesting that polyunsaturated fatty acids contribute to increased cancer cell growth. Our study strongly suggests that unregulated LDLR expression is at least one of the mechanisms by which cancer cells acquire extra essential fatty acids for eicosanoid synthesis and growth stimulation. It linked the lack of feedback regulation of LDLR to increased prostate cancer risk from dietary fat. We also showed, for the first time, that a member of the SREBP family is feedback regulated by cholesterol in normal cells, but not in cancer cells. The data on feedback regulation of SREBP2 may lead to an understanding of the mechanism by which cancer cells escape sterol feedback regulation.

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